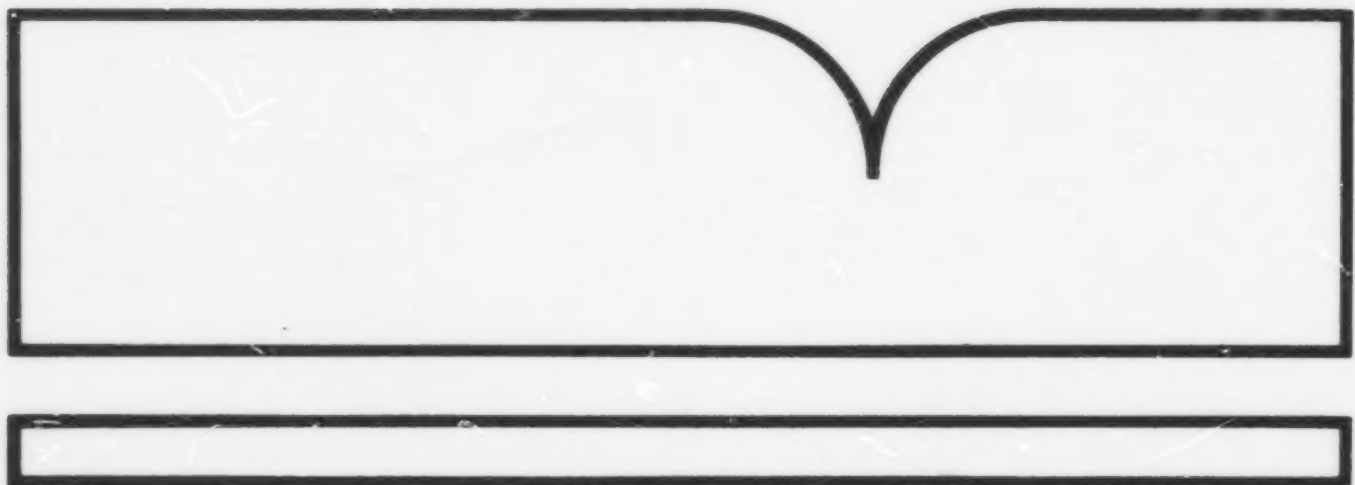


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Health and Environmental
Effects Profile for 2-Ethoxyethanol

(U.S.) Environmental Protection Agency
Cincinnati, OH

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR 2-ETHOXYETHANOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT The Health and Environmental Effects Profile for <u>2-ethoxyethanol</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>2-Ethoxyethanol</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>2-ethoxyethanol</u> is <u>25 mg/day</u> for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on ~~acute~~ chronic toxicity. The RQ value for <u>2-ethoxyethanol</u> is <u>1000</u>.		
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
GC/MS	Gas chromatography/mass spectrometry
HPLC	High pressure liquid chromatography
IC ₅₀	Concentration required to immobilize 50% organisms
i.p.	Intraperitoneal
i.v.	Intravenous
K _{oc}	Soil sorption coefficient standardized with respect to organic carbon
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MEC	Minimum effective concentration
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RQ	Reportable quantity
RV _d	Dose rating value
RV _e	Effect rating value

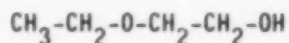
LIST OF ABBREVIATIONS (cont.)

S.C.	Subcutaneous
SPF	Specific pathogen free
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Ethoxyethanol is the common chemical name, but this compound is also known by the synonyms ethylene glycol monoethyl ether, glycol ethyl ether, ethyl glycol and hydroxy ether. Trade names for 2-ethoxyethanol include Dowanol 2-ethoxyethanol, Cellosolve, Oxitol and Poly-solv 2-ethoxyethanol. The structure, molecular weight, empirical formula and CAS number for 2-ethoxyethanol are as follows:



Molecular weight: 90.12

Empirical formula: $\text{C}_4\text{H}_{10}\text{O}_2$

The CAS Registry number for this compound is 110-80-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Ethoxyethanol is a colorless liquid at room temperatures (Verschueren, 1983). The odor has been described as slightly pleasant (U.S. EPA, 1981), practically odorless (Hawley, 1977), and sweet, musty, unpleasant to pleasant (Verschueren, 1983). 2-Ethoxyethanol is completely soluble with water and with many organic solvents (NIOSH, 1983). Selected physical properties are as follows:

Freezing point:	-148°F (-70°C)	Dow Chemical Co., 1981
Boiling point (760 mm Hg):	135.5°C	Dow Chemical Co., 1981
Specific gravity (25/25°C):	0.928	Dow Chemical Co., 1981
Vapor pressure at 20°C	3.8 mm Hg	Verschueren, 1983
at 25°C	5.5 mm Hg	Dow Chemical Co., 1981
at 30°C	7.0 mm Hg	Verschueren, 1983

Water solubility:	complete	Dow Chemical Co., 1981
Evaporation Rate (butyl acetate = 1.0)	0.35	Dow Chemical Co., 1981
Log octanol/water partition coefficient:	-0.10 (recommended value)	Hansch and Leo, 1981
Flash point (TCC):	109°F	Dow Chemical Co., 1981
Conversion factor (air):	1 mg/m ³ =0.27 ppm 1 ppm=3.75 mg/m ³	Verschueren, 1983

2-Ethoxyethanol is combustible and presents a moderate fire risk (Hawley, 1977). It is highly reactive in the presence of strong oxidizers (NIOSH, 1983). Glycol ethers, such as 2-ethoxyethanol, undergo most of the reactions that are typical of alcohols (Dow Chemical Co., 1981).

1.3. PRODUCTION DATA

2-Ethoxyethanol is currently manufactured on a commercial scale by the following companies (SRI, 1984):

Eastman Kodak (Texas Eastman)	Longview, TX
ICI Americas	Bayport, TX
Shell Oil Co.	Geismar, LA
Texaco	Port Neches, TX
Union Carbide	Penuelas, PR

Domestic production of 2-ethoxyethanol in the years 1981, 1982, and 1983 has been reported to be 205.6, 178.2, and 187.5 million pounds, respectively (USITC, 1982, 1983, 1984). During 1983, 64.8 million pounds of 2-ethoxyethanol were exported (U.S. Dept. of Commerce, 1984).

Commercial production of 2-ethoxyethanol involves reacting ethylene oxide with an excess of ethanol in the presence of an acidic or a basic catalyst followed by vacuum-fractionation (U.S. EPA, 1981).

1.4. USE DATA

Excluding exports, the following use pattern for 2-ethoxyethanol has been reported (Lawler, 1977):

Production of 2-ethoxyethanol acetate	41.7%
Solvent for protective coatings	41.6%
Solvent for printing inks	4.8%
Other solvent uses	11.9%

As a protective coating solvent, 2-ethoxyethanol is used in nitrocellulose lacquers and epoxy coatings for industrial finishes, in alkyd coatings for interior and exterior paints, automotive and machinery finishes, traffic paints, and in phenolic coatings for interior and exterior varnishes, wire enamels, and metal containers (U.S. EPA, 1981). The other uses include applications as a solvent in adhesives, metal cleaners, glass cleaners, and leather dyeing operations, as a diluent in hydraulic brake fluids, and as an extractant in the manufacture of pharmaceuticals (U.S. EPA, 1981). Use as an anti-icing agent for aviation fuels has also been cited (Hawley, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Like other chemicals, the fate of 2-ethoxyethanol in the environment will depend on the ability of the compound to undergo chemical, photochemical and biological reactions and to transport or partition from one environmental matrix into another. The individual fate processes in water, air and soil environments are discussed below.

2.1. WATER

2.1.1. Hydrolysis. Glycols, ethers and alcohols are generally resistant to hydrolysis (Lyman et al., 1982). Experimental hydrolysis data regarding 2-ethoxyethanol were not located, however, hydrolysis of 2-ethoxyethanol in the aquatic environment is not expected to be important.

2.1.2. Oxidation. The rate constant for the reaction between 2-ethoxyethanol and hydroxyl radicals in aqueous solution at room temperatures has been reported to be $1 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Anbar and Neta, 1967) and $1.68 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Dorfman and Adams, 1973). Assuming an aquatic OH radical concentration of 10^{-17} M , the half-life is estimated to be >1 year. Therefore, this reaction has no significant environmental importance.

Data pertaining to the aquatic reaction between 2-ethoxyethanol and singlet oxygen or RO_2 radicals were not located.

2.1.3. Photolysis. Data pertaining to the photolysis of 2-ethoxyethanol in aqueous solution were not located in the available literature cited in the Appendix.

2.1.4. Microbial Degradation. The Dow Chemical Co. (1981) has reported 5-, 10- and 20-day BODTs for 2-ethoxyethanol of 62, 77 and 81%. A 20-day BODT >50% indicates the product will largely be removed in a biological wastewater treatment plant while a 20-day BODT of 10-50% indicates it will be partially removed (Dow Chemical Co., 1981).

Using an effluent from a biological sanitary waste treatment plant, Bridie et al. (1979a) determined 5-day BODTs of 53 and 65% for 2-ethoxyethanol in non-acclimated and in acclimated seed, respectively. Price et al. (1974) used a settled domestic wastewater seed to examine the biodegradation of 2-ethoxyethanol in fresh and saltwater. In freshwater, 5- and 20-day BODTs of 36 and 100% were measured, respectively, while in saltwater the respective 5- and 20-day BODTs were 5 and 62%. Zahn and Wellens (1980) observed 2-ethoxyethanol degradation in excess of 90% in 5.5 days (3 days of acclimation) in a batch activated sludge system.

Bogan and Sawyer (1955) determined 5-day BODTs of 7.6% in a sewage seed and 54.3% in an acclimated activated sludge seed for 2-ethoxyethanol. Mills and Stack (1954) determined a 10-day BODT of 83.3% for 2-ethoxyethanol in an activated sludge seed.

Ellis et al. (1956) conducted pure culture biodegradation studies with 2-ethoxyethanol utilizing microbes isolated from industrial emulsions. Rapid degradation was observed with Pseudomonas 324, moderate degradation with P. oleovorans, and no degradation with P. brevis or P. formicans.

2.1.5. Transport.

2.1.5.1. VOLATILIZATION -- The vapor-liquid equilibrium of water and 2-ethoxyethanol at 760 mm Hg has been determined by the Dow Chemical Co. (1981). When the percent by weight of 2-ethoxyethanol in the liquid-phase is <5%, the percent by weight of 2-ethoxyethanol in the vapor-phase is roughly twice the percent in the liquid-phase. Therefore, the air-to-water ratio is ~2, which is the value of the unitless Henry's Law Constant. Conversion to units yields a Henry's Law Constant of 4.8×10^{-2} atm-m³/mole. This value of Henry's Law Constant indicates that volatilization is both significant and rapid in the aquatic environment (Lyman et al., 1982). Even

though 2-ethoxyethanol is completely miscible in water, the vapor-liquid equilibrium suggests significant 2-ethoxyethanol evaporation from water.

2.1.5.2. ADSORPTION -- Experimental adsorption data were not located. The complete water solubility and low octanol/water partition coefficient of 2-ethoxyethanol suggest that adsorption to particulate organic matter and sediment in water will not be environmentally important.

2.1.5.3. BIOACCUMULATION -- Experimental bioaccumulation data were not located. The complete water solubility and low octanol/water partition coefficient of 2-ethoxyethanol suggest that significant bioaccumulation in aquatic organisms is not expected to occur. The BCF may be estimated from the K_{ow} by use of the equation (Veith et al., 1980): $\log BCF = 0.76 \log K_{ow} - 0.23$. On the basis of a $\log K_{ow}$ value of -0.10 (see Section 1.2.), the BCF value is calculated to be 0.5. This value suggests insignificant bioaccumulation of 2-ethoxyethanol in aquatic organisms.

2.2. AIR

2-Ethoxyethanol has demonstrated a fairly high reactivity in smog chamber studies in which the compound was irradiated (via black lights and sunlamps) in combination with nitrogen oxides (Yanagihara et al., 1976, 1977; Joshi et al., 1982; Levy, 1973). In one study (Joshi et al., 1982), irradiation of a ratio of 2:1 (2-ethoxyethanol: NO_x) demonstrated a half-life of 9.8 hours for 2-ethoxyethanol. The reactivity of 2-ethoxyethanol in a smog chamber study was found to fall between xylene and toluene (Yanagihara et al., 1976).

An experimentally derived rate constant for the reaction of 2-ethoxyethanol with hydroxyl radicals in air was not located. Guesten et al. (1981) derived a method of estimating gas-phase reaction of OH radicals from corresponding rate constants in water; the rate constant for the reaction of

2-ethoxyethanol with OH radicals in water is $1 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Anbar and Neta, 1967) which predicts (by the method of Guesten et al., 1981) a gas-phase rate constant of $\sim 3 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$. Assuming an average atmospheric OH radical concentration of $10^6 \text{ molecules/cm}^3$, a half-life of ~ 4 days can be calculated.

2-Ethoxyethanol does not react with ozone (Joshi et al., 1982). Pertinent data regarding direct photolysis was not located in the available literature cited in the Appendix.

2.3. SOIL

2.3.1. Microbial Degradation. Fincher and Payne (1962) isolated a bacterial microbe from soil which had been enriched with triethylene glycol and found that the microbe (a gram-negative asporogenous rod) was capable of using 2-ethoxyethanol as a sole source of carbon for rapid aerobic growth. Other soil microbial studies specific to 2-ethoxyethanol were not located.

2.3.2. Chemical Degradation. Eltantawy and Arnold (1973) have determined that 2-ethoxyethanol undergoes rapid catalytic degradation at a temperature near the boiling point of 2-ethoxyethanol when the compound is contacted with the clay illite. Whether this clay catalyzed decomposition can occur in the soil environment is not known.

2.3.3. Leaching. The complete WS and K_{ow} of 2-ethoxyethanol suggest that it may be readily leached in the soil environment, although there is no experimental data available to confirm this prediction. Molecular topology and quantitative structure-activity relationship analysis, via the method cited by Sabljic (1984), predicts a soil sorption coefficient (K_{oc}) for 2-ethoxyethanol of 113 indicating moderate soil mobility.

2.3.4. Volatilization. In a standard evaporation test conducted at 77°F and 15% relative humidity, 2-ethoxyethanol was found to experience a 100%

weight loss in 20 minutes (Dow Chemical Co., 1981). This suggests that 2-ethoxyethanol will evaporate quite rapidly from dry soil, assuming no significant inhibiting effect from potential adsorption. Evaporation from moist soils may also be significant.

2.4. SUMMARY

In the aquatic environment, 2-ethoxyethanol is expected to volatilize from water bodies quite rapidly. It is also susceptible to significant microbial degradation in biological treatment facilities; the importance of microbial degradation in natural waters is not clear. Hydrolysis and oxidation are not expected to be aquatically important. 2-Ethoxyethanol is not expected to bioaccumulate in aquatic organisms based on its WS and K_{ow} data.

In the atmosphere, 2-ethoxyethanol appears to be susceptible to significant degradation by hydroxyl radicals. Isolated soil microbes have been shown to be able to grow rapidly on 2-ethoxyethanol, but the importance of microbial decomposition in the soil environment has not been demonstrated. 2-Ethoxyethanol may undergo moderate leaching in soil.

3. EXPOSURE

3.1. WATER

Shackelford and Keith (1976) have reported the detection of 2-ethoxyethanol (no concentrations reported) in the effluents from chemical facilities in Brandenburg, KY (during February 1974) and from an unnamed chemical facility effluent (during October 1975). The U.S. EPA STORET Data Base contains only one observation for 2-ethoxyethanol; an effluent from the Olin Corporation facility in Brandenburg, KY was found to have a concentration of 0.10 $\mu\text{g/l}$ on February 8, 1974. Yasuhara et al. (1981) detected 2-ethoxyethanol levels of 250-1200 ppb in the Hayashida River in Japan which is predominantly contaminated by effluents from the leather industry.

The major environmental release of 2-ethoxyethanol to the aquatic environment is expected to result from wastewater effluents from production and use plants (U.S. EPA, 1981).

3.2. FOOD

Pertinent data regarding the presence of 2-ethoxyethanol in foods were not located in the available literature cited in the Appendix.

3.3. INHALATION

A major environmental release of 2-ethoxyethanol to air is expected to result from emissions from production and use plants (U.S. EPA, 1981). Emissions from consumer products, such as paints and varnishes, are also expected to cause atmospheric exposures. As many as 400,000 workers in the U.S. are potentially exposed to 2-ethoxyethanol (NIOSH, 1983). The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for 2-ethoxyethanol is 200 ppm while the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a TLV of 50 ppm as of 1984 which may be changed to 5 ppm (Clapp et al., 1984).

Monitoring data for 2-ethoxyethanol in the general ambient atmosphere were not located in the available literature cited in the Appendix.

3.4. DERMAL

Consumers may be exposed to 2-ethoxyethanol skin contact through use of products, such as paints, which contain the compound. However, the extent to which exposure occurs is not clear (U.S. EPA, 1981).

4. PHARMACOKINETICS

4.1. ABSORPTION

Although few direct absorption data are contained in the available literature, oral, inhalation and dermal absorption can be inferred from the well-established toxicity of 2-ethoxyethanol in experimental animals (see Chapter 5).

A study by Dugard et al. (1984) examined the absorption of several glycol ethers across isolated human abdominal epidermis in vitro. 2-Ethoxyethanol was readily absorbed and had a rate of absorption of 0.796 mg/cm²/hour. Hardin et al. (1984) demonstrated embryotoxic and teratogenic effects of 2-ethoxyethanol cutaneously applied to the backs of pregnant Sprague-Dawley rats, thus supporting absorption through the skin as a viable route of exposure.

Orally administered 2-ethoxyethanol is rapidly absorbed through the gastrointestinal tract as up to 71.6% of radioactivity from ¹⁴C-2-ethoxyethanol was recovered in the urine within 24 hours (Cheever et al., 1984). Jonsson et al. (1982) also found 2-ethoxyethanol metabolites in the urine after both oral and inhalation exposure. Shell Oil (1978) reported that potentially toxic amounts of 2-ethoxyethanol are readily absorbed through the skin. It appears, therefore, that the gastrointestinal tract, lung, and skin all represent viable routes of exposure and must be considered when evaluating the health hazard posed by 2-ethoxyethanol.

4.2. DISTRIBUTION

Following administration of 2-ethoxyethanol [ethanol-1,2-¹⁴C] by gavage to male Sprague-Dawley rats, testicular levels of the label peaked at 2 hours (0.31% of dose) followed by a rapid decline to only 0.06% of the dose after 6 hours. The radioactive metabolite in the testes was identified

as ethoxyacetic acid, which may represent the toxic species. Therefore, although the testes have been shown to be more sensitive to 2-ethoxyethanol (Section 5.4.), it does not appear that this organ sequesters 2-ethoxyethanol or its metabolites (Cheever et al., 1984).

Shaffer et al. (1980) reported that low molecular weight glycol ethers were not found in extracellular fluids and had a clearance rate from plasma similar to that of creatinine.

4.3. METABOLISM

One form of human liver alcohol dehydrogenase was shown to use 2-ethoxyethanol as a substrate with a K_m of 6×10^{-4} M and a maximal velocity 44% that of ethanol (Blair and Vallee, 1966). This lends support to the proposed pathway of 2-ethoxyethanol oxidation to its corresponding acetaldehyde.

A study by Foster et al. (1983) demonstrated that equimolar amounts of 2-ethoxyethanol and its acetic acid derivative produced similar testicular lesions. This further strengthens the hypothesis that the metabolism of 2-ethoxyethanol proceeds via an acetaldehyde moiety to the corresponding acid and suggests that this product may be the ultimate toxic species.

Urinary metabolites excreted by male Sprague-Dawley rats dosed orally with 230 mg/kg 2-ethoxyethanol[ethoxy-1- ^{14} C] or 2-ethoxyethanol[ethanol-1,2- ^{14} C] were analyzed by HPLC and scintillation spectrometry. Two metabolites were responsible for 72.9% and 75.5% of the administered dose of the ethoxy- and ethanol-labeled compounds, respectively. These metabolites were identified as ethoxyacetic acid and N-ethoxyacetyl glycine and together they accounted for 94% (ethanol-labeled) and 97% (ethoxy-labeled) of the total radioactivity recovered in the urine. Ethoxyacetic acid was the more abundant of the two metabolites, comprising 43.4% and 44.9% of the dose of the ethanol and ethoxy derivatives, respectively. This study demonstrates

that the primary metabolic pathway for 2-ethoxyethanol involves oxidation to the acid derivative followed by partial glycine conjugation. Cleavage of the ether linkage was also suggested, as evidenced by the minor but significant recovery of $^{14}\text{CO}_2$ (Cheever et al., 1984).

Jonsson et al. (1982) compared the urinary metabolic profile in albino rats treated orally with 9.3 or 93 mg 2-ethoxyethanol or exposed by inhalation to 37 g/m³ 2-ethoxyethanol for 1 hour. Two metabolites were identified as ethoxyacetic acid and N-ethoxyacetyl glycine in the urine of all three treated groups. Although the two metabolites accounted for only 30% of the given dose, these findings support the previously described metabolic pathway.

Although 2-ethoxyethanol has a higher affinity for alcohol dehydrogenase than ethanol in vitro (Blair and Vallee, 1966), the simultaneous ingestion of 104 g ethanol and inhalation of 0-316 ppm 2-ethoxyethanol did not affect the elimination of ethanol in a human volunteer (Pederson et al., 1980). Figure 4-1 outlines the proposed metabolic pathways for 2-ethoxyethanol.

4.4. EXCRETION

Male Sprague-Dawley rats (190-210 g) were orally dosed with either 230 mg/kg 2-ethoxyethanol[ethanol-1,2- ^{14}C] or 2-ethoxyethanol[ethanol-1- ^{14}C]. After 96 hours, 85.4% and 77.8% of the ethanol- and ethoxylabeled derivatives, respectively, were recovered in the urine. Most of the radioactivity (71.6% and 69.9%, respectively) was excreted in the urine within the first 24 hours. Differences in the elimination of radioactivity as respiratory $^{14}\text{CO}_2$ were observed depending upon position of the label. The ethanol-labeled compound yielded 4.6% of the administered radioactivity as $^{14}\text{CO}_2$ after 30 hours, while the ethoxy-labeled species resulted in the 11.7% of the dose as respiratory $^{14}\text{CO}_2$. The amount of label

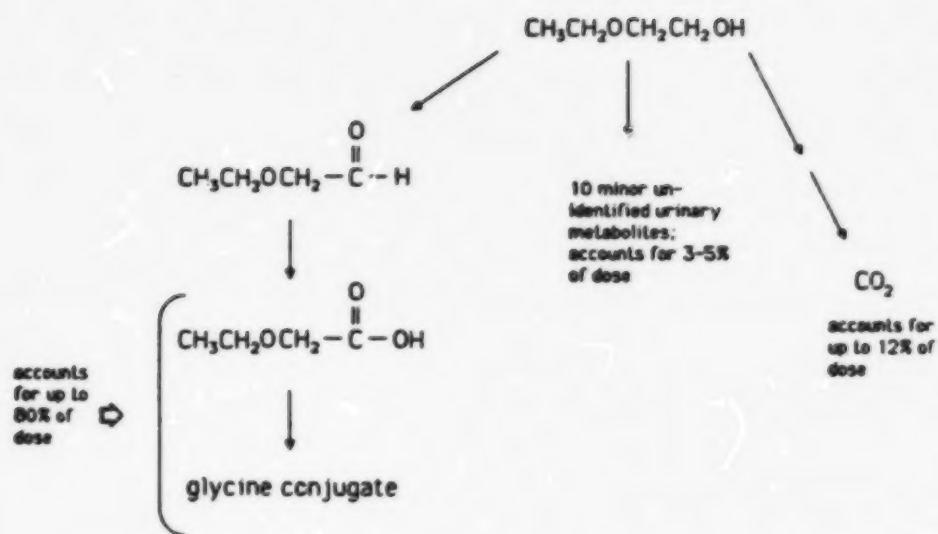


FIGURE 4-1
 Proposed Metabolic Scheme for 2-Ethoxyethanol
 Source: ECETOC, 1985

recovered in volatile organics, feces and carcass was minimal when compared to urinary excretion. Total recovery of label was 99.3% for the ethanol-labeled compound and 94.4% for the ethoxy-labeled compounds. Biological half-times were calculated to be 12.5 and 9.9 hours for the ethanol and ethoxy derivatives, respectively (Cheever et al., 1984).

5. EFFECTS

5.1. CARCINOGENICITY

A 2-year study using male and female Fischer 344/N rats and B6C3F1 mice was conducted under the auspices of the National Toxicology Program (NTP) (Melnick, 1984). Animals were administered 2.0, 1.0, or 0.5 g/kg 2-ethoxyethanol by gavage 5 days/week for 103 weeks. Since 2.0 g/kg was generally lethal, surviving animals in this group were sacrificed by the 18th week of the study. Although the Pathology Working Group is currently reviewing the histology (NTP, 1985) no increase in tumor incidence at any dose level in any of the animal groups was reported (Melnick, 1984). No tumors were observed in rats given 1.45% 2-ethoxyethanol in the diet (equivalent to 725 mg/kg/day) in a 2-year study conducted by Morris et al. (1942).

5.2. MUTAGENICITY

Reverse mutation assays using Salmonella typhimurium and Escherichia coli have been conducted with 2-ethoxyethanol and are summarized in Table 5-1. In a plate incorporation assay using S. typhimurium strains TA1537, TA1535, TA100 and TA98 with and without S-9 from Aroclor-induced rats, 2-ethoxyethanol did not produce reversions at concentrations up to 23 mg/plate (Ong, 1980). Ong et al. (1980) using the same strains of S. typhimurium with and without metabolic activation also observed no excess reversions at concentrations up to 20 μ l 2-ethoxyethanol/plate. Similar results were obtained by Zeiger et al. (1982) who used the same strains of S. typhimurium, S-9 from Aroclor 1254-induced male rats and hamsters and 2-ethoxyethanol dissolved in water at concentrations of 10-25 μ l/plate. Kawalek and Andrews (1980) also obtained negative results using strain TA1538.

TABLE 5-1
Mutagenicity of 2-Ethoxyethanol

Assay	Indicator/ Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	<i>Salmonella typhimurium</i> TA1537, TA1535 TA100, TA98	plate incorporation	up to 23 mg/plate	± S9 from Aroclor-induced rats	-	NC	Org. 1980
Reverse mutation	<i>S. typhimurium</i> TA1537, TA1535 TA100, TA98	plate incorporation	up to 20 µg/plate	± metabolic activation (not specified)	-	NC	Org. 1980
Reverse mutation	<i>S. typhimurium</i> TA1537, TA1535 TA100, TA98	plate incorporation	0.1-10 mg/plate	± S9 from Aroclor 1254 induced male Sprague-Dawley rats and Syrian hamster.	-	NC	Zelger et al., 1982
Reverse mutation	<i>Escherichia coli</i> Sd-4-73	paper-disk method	0.01-0.025 mg/plate	None	-	The increase in the frequency of rever- sion to streptomycin independence was <50%. The compound was thus judged to be nonmuta- genic.	Szybalski, 1958
Reverse mutation	<i>S. typhimurium</i> TA1538	plate incorporation	3.5 mg/plate	± S9 from Aroclor 1254 and pheno- barbital-induced male Sprague- Dawley rats	-	NC	Kavalek and Andrews, 1980
Mammalian in vitro, sister chromatid exchange	Chinese hamster ovary cells	cell culture	NR	± rat S9 mix	+/+	Weaker response with S9	ECETOC, 1985
Mammalian in vitro, chromosomal aberrations	Chinese hamster ovary cells	cell culture	NR	± rat S9 mix	+/+	Weaker response with S9	ECETOC, 1985
Sex-linked recessive lethal	<i>Drosophila melanogaster</i> , 3 days old	feeding, injection	NR	NA	-	NC	ECETOC, 1985

NR = Not reported; NA = not applicable; NC = no comment

A paper-disk assay using E. coli strain Sd-4-73 and 2-ethoxyethanol concentrations of 10-25 μ l/plate also produced negative results. In this test, 2-ethoxyethanol displayed a relative mutagenicity, defined as the ratio of the number of streptomycin-independent colonies on the mutagen plate to the number of colonies on the control plate, of <1.5 and was thus considered nonmutagenic (Szybalski, 1958).

Unpublished results from NTP have yielded positive results in SCE and chromosomal aberration assays using CHO cells. However, these studies were cited only in tabular form by ECETOC (1985) and their value cannot adequately be evaluated in this profile. In summary, however, it is generally concluded that 2-ethoxyethanol, along with other glycol ethers, does not pose a significant genotoxic hazard.

5.3. TERATOGENICITY

Andrew et al. (1981) demonstrated a significant increase in soft tissue and skeletal abnormalities in rabbit fetuses following exposure of pregnant does to 160 ppm 2-ethoxyethanol for 7 hours/day during days 1-18 of gestation. A high dose group (615 ppm) exhibited 100% embryomortality. Maternal toxicity at the low dose was minimal; the fetuses, however, displayed a statistically significant ($p \leq 0.05$) increase in the number of major malformations such as ventral wall defects (omphalocele, split peritoneum and umbilical hernia) and fused aorta and pulmonary artery, minor anomalies characterized by polycystic condition and fused kidneys, and skeletal changes including supernumerary ribs, accompanied by vertebral and sternebral variations. In the same study, female rats were exposed to air, 150 ppm 2-ethoxyethanol or 649 ppm 2-ethoxyethanol, 7 hours/day, 5 days/week for 3 weeks, mated and exposed to 0, 202 or 767 ppm 2-ethoxyethanol through gestation day 19. As with rabbits, the high dose rats had 100% resorptions,

while exposure to 202 ppm resulted in ~25% depressed fetal body weight and 10% reduced crown-rump length. There was also a significant increase in minor anomalies characterized by cardiovascular defects and skeletal variants (primarily supernumerary ribs and reduced ossification) in this same group.

Pregnant Sprague-Dawley rats were exposed to 100 ppm (369 mg/m³) 7 hours/day during gestation days 7-13 or 14-20 (Nelson et al., 1981). Various behavioral tests were performed on exposed neonates to evaluate neuromuscular function, exploratory and circadian activity, aversive, and appetite learning. In pups of dams exposed during day 7-13, performance on a rotorod indicated that neuromuscular ability was inhibited significantly. In addition, these pups had an increased latency period for leaving the central area of an open field, but showed somewhat better learning ability in an avoidance task at 34 days of age. Offspring from dams exposed on gestation days 14-20 were significantly less active in an activity wheel and performed less well in avoidance conditioning begun at 60 days of age than controls. This study also measured the levels of several neurotransmitters in various regions of the brain in newborn and 21-day old pups. In newborns, norepinephrine levels were depressed to a greater extent in whole brain homogenates from the 7-13 day group as compared to the 14-20 day animals, although both exposure groups had levels significantly lower than controls. Twenty-one-day old pups from dams exposed on days 7-13 had significantly increased levels of norepinephrine in the cerebrum, brainstem, and midbrain, acetylcholine in the cerebrum, cerebellum, and midbrain, and dopamine in the cerebrum. Twenty-one-day old pups in the 14-20 day exposure group had significant increases in acetylcholine, dopamine and serotonin levels only in the cerebrum. It is noteworthy that the bulk of neurochemi-

cal variations occurred in the cerebrum, which is associated with more complex tasks such as learning behavior. This study demonstrates that there are clear functional and chemical deficits in offspring of dams exposed to only 100 ppm 2-ethoxyethanol and that fetuses appear to be more sensitive in the earlier (7-13 days) stages of gestation (Nelson et al., 1981).

The Chemical Manufacturers Association Glycol Ethers Program Panel (CMA, 1983) advised caution when interpreting this study since effects noted in those offspring exposed during gestation days 7-13 differed from those in animals exposed during days 14-20. The significance of the neurochemical alterations as well as the interpretation of the performances on several of the behavioral tasks were also questioned. Corroborating evidence was strongly suggested in order to evaluate this study more completely.

In a related study, Nelson et al. (1982a,b) investigated the interaction between ethanol consumption and 2-ethoxyethanol exposure. Gravid Sprague-Dawley rats were exposed by inhalation to 200 ppm 2-ethoxyethanol, alone, 7 hours/day during gestation days 7-13 [the period of maximal susceptibility as determined from the Nelson et al. (1981) study], 10% ethanol in the drinking water during gestation days 7-13 or 14-20, or 10% ethanol and 100 ppm 2-ethoxyethanol during early or late gestation. The 200 ppm exposed offspring demonstrated an altered ability on an ascent test, decreased performance on the rotorod, decreased activity in an open field test, and consistently sub-average performance in an avoidance-conditioning task. The decreased neuromuscular activity was also observed at 100 ppm to a lesser degree. Ethanol, which is presumed to follow the same metabolic pathway as 2-ethoxyethanol (see Section 4.3.), inhibited these behavioral effects when given early in gestation (days 7-13) and enhanced the effects when administered during gestation days 14-20 (Nelson et al., 1982a).

Neurochemical alterations in the brains of neonates and 21-day-old pups were also examined in the same study (Nelson et al., 1982b). Exposure to 200 ppm 2-ethoxyethanol by inhalation during gestation days 7-13 significantly altered the levels of acetylcholine, dopamine and norepinephrine in the cerebrum as well as the amounts of acetylcholine and dopamine in the midbrain and the level of norepinephrine in the cerebellum in 21-day-old pups. These variations were also observed in pups from 100 ppm exposed dams (Nelson et al., 1981). Deviations were seen in the brainstems of 21-day-old rats and in whole brain homogenates in neonates from 100 ppm dams, but not 200 ppm dams. As with behavioral parameters, ethanol depressed the variations in neurotransmitter levels when administered early in gestation and potentiated the effects later in gestation.

A study by Doe (1984a) examined the effects of inhalation exposure to 10 ppm, 50 ppm, or 250 ppm 2-ethoxyethanol for 6 hours/day during days 6-15 of gestation on Wistar Alpk AP rats. Only the 250 ppm exposure group showed a statistically increased incidence of minor visceral defects such as renal pelvic dilation. This group also had a significant increase in the occurrence of minor skeletal defects (97.5%), related mostly to reduced ossification, although the control group had a substantial percentage of fetuses having these aberrations (46.3%). Dutch rabbits were exposed by inhalation to 10, 50 or 175 ppm 2-ethoxyethanol 6 hours/day during gestation days 6-18. The only statistically significant increase occurred in the 175 ppm exposure group, which had greater numbers of minor skeletal defects and variants (64.5% and 79.1%, respectively). As with rats, the control group also exhibited a marked incidence of these defects (32.4% for minor defects and 51.5% for skeletal variants). This study concluded that no terata were observed in rats at levels up to 250 ppm, 6 hours/day, although this level was fetotoxic and caused slight maternal toxicity [significant decreases in

hemoglobin and hematocrit levels (authors' statement)]. Mild fetotoxicity was observed at 50 ppm. In rabbits, 175 ppm, 6 hours/day appeared to be close to a threshold level for teratogenicity while no effects were observed at 50 ppm.

Pregnant SPF Sprague-Dawley rats were treated cutaneously with 0.25 mL (233 mg) 2-ethoxyethanol 4 times daily on days 7-16 of gestation and necropsied on day 21. There were statistically significant increases in visceral malformations, most notably cardiac and renal alterations. A wide range of skeletal anomalies were also observed including vertebral and rib variations and reduced ossification (Hardin et al., 1984).

Hardin et al. (1982) tested the teratogenic effects of dermally applied 2-ethoxyethanol in SPF Sprague-Dawley rats. Undiluted 2-ethoxyethanol was applied to the shaved interscapular region 4 times/day at a high (0.50 mL/application, 2.0 mL/day) and low (0.25 mL/application, 1.0 mL/day) dose during gestation days 7-16. A dose-related decrease in maternal body weight gain was observed. There was also a significant reduction in liver weight and a significant increase in kidney weight in dams exposed to the higher dose. The body weight changes were associated most probably with the dose-related increased incidence of resorbed litters. Only 52% of the dams exposed to the low 2-ethoxyethanol dose had live fetuses, and the number of live fetuses per litter and the mean fetal weights were severely depressed. In the high dose group, every litter was completely resorbed. Fetal examination revealed a significantly increased incidence of cardiovascular, renal and CNS anomalies and a number of skeletal alterations in the 0.25 mL treatment groups compared with controls. Three fetuses also exhibited imperforate anus and acaudia. Thus, as with inhalation exposure, 2-ethoxyethanol administered dermally can cause a high degree of embryoletality and teratogenicity at doses that are marginally toxic to the dams.

Oral treatment of Sprague-Dawley rats at 200 mg 2-ethoxyethanol/kg/day during gestation days 7-9 or 10-12 produced decreased fetal weights and increased incidences of skeletal and cardiovascular anomalies similar qualitatively to those seen in animals exposed for longer periods. Dams exposed on gestation days 7-15, had a significant decrease in weight gain, and ~25% of the fetuses from these mothers had malformations compared to none in the control group. Fetal mortality also was increased in this treatment group (Goad and Cranmer, 1984).

Reproductive toxicology was investigated in mice, rats, and rabbits by Stenger et al. (1971). Swiss white mice were treated with 2-ethoxyethanol s.c. at concentrations of 0, 50 or 100 μ L/kg/day during gestation days 1-18. Wistar rats were also treated similarly with 0, 25, 50 or 100 μ L/kg/day during days 1-21 of gestation while another group of rats received 0, 12.5, 25, 50, 100, 200, or 400 μ L/kg/day via stomach tube during the same period of pregnancy. Yellow silver rabbits were administered 0 or 25 μ L/kg/day 2-ethoxyethanol s.c. during days 7-16 of gestation. In the orally treated rats, there was an increase in resorptions at 400 μ L/kg/day, an increase in fetal mortality at 200 μ L/kg/day dose and a corresponding decrease in mean fetal weight at the three highest dose levels. No evidence of an increased incidence of malformations was found in mice or rabbits at any dose level. On the other hand, rats had a dose-related increase in skeletal abnormalities that first become evident at the 100 μ L/kg dose level in both the s.c. and oral treatment groups.

5.4. OTHER REPRODUCTIVE EFFECTS

Foster et al. (1983) examined the testicular effects of oral doses of 250, 500 or 1000 mg/kg/day 2-ethoxyethanol administered to 4-week-old Sprague-Dawley rats over an 11 day period. While the relative organ weights

of the prostate and seminal vesicles were similar to controls at all time points and all dose levels, there were significant reductions in relative testis weights on day 11 at the two higher doses. Histological examination of the testes in these animals revealed significant degeneration of primary spermatocytes (Creasy and Foster, 1984).

The Fertility Assessment by Continuous Breeding protocol developed by the National Toxicology Program was utilized by Lamb et al. (1984) to evaluate the reproductive toxicity of 2-ethoxyethanol in male and female CD-1 mice. Eleven-week-old animals were administered either 0.5, 1.0 or 2.0% 2-ethoxyethanol in the drinking water for 7 days prior to mating and then for 14 weeks during a period of continuous breeding. There were no litters produced by animals exposed to 2% 2-ethoxyethanol while the 1% group, which had a fertility index of 90%, demonstrated a statistically significant reduction in the number of litters per fertile pair, live pups per litter, proportion of pups born alive, and live pup weight. Crossover mating trials to determine the sex affected by the exposure showed that females treated with 2% 2-ethoxyethanol produced no litters, while high dose males had statistically fewer successful matings (fertility index of 28% compared to 85% for controls). At the 1% level, both males and females had reduced fertility although the results were not statistically significant. Histological examinations of all reproductive tissues revealed no gross or microscopic lesions in females, dose-related reductions in testes weight and sperm motility in males exposed to 2% 2-ethoxyethanol. A significant dose-related increase in the percentage of morphologically abnormal sperm was observed in both the 1 and 2% treatment groups. In addition, there were marked, though not statistically significant, reductions in epididymal and caudal weights in the high-dose treatment group. Drinking water consumption

data for males revealed that the 1 and 2% groups received ~1500 and 2600 mg/kg 2-ethoxyethanol/day, respectively. Schuler et al. (1984) orally dosed CD-1 mice with 3605 mg/kg (the previously established maternal LD₁₀) during days 7-14 of gestation and observed no viable litters.

A single 3-hour exposure of Alpk/Alp Wistar derived rats to 4500 ppm 2-ethoxyethanol resulted in a mean 20% reduction in relative testis weight 15 days after exposure (Doe, 1984b). Hematuria was also observed in these animals.

Zenick et al. (1984) assessed 2-ethoxyethanol-induced spermatotoxic effects by evaluating sperm recovered from the female genital tract shortly after mating. Male Long-Evans hooded rats were given 0, 936, 1972 or 2808 mg/kg 2-ethoxyethanol orally for 5 days (week 1). Semen samples were obtained and analyzed at weeks, 0, 1, 4, 7, 10 and 14. By week 4, males in the middle and high dose group had significantly depressed sperm counts. Measurements at week 7 showed the low dose group also had significantly depressed sperm counts, while the two other treatment groups exhibited azoospermia. After the seventh week all rats gradually recovered to near-baseline levels, and by week 16 recovery was essentially complete. In the middle dose group, the epididymal weight was significantly reduced relative to controls. In a related experiment, male rats were intubated with 0 or 936 mg/kg 2-ethoxyethanol, 5 days/week for 6 weeks. Semen evaluations were performed weekly. The treated rats had a significantly reduced increase in body weight throughout the exposure period, significantly higher brain and spleen weights and reduced hematocrit and hemoglobin after 6 weeks. A significant depression in sperm counts and in the percentage of morphologically normal sperm was observed by the fifth week of exposure, while alterations in sperm motility were evident by the sixth week. In addition, caudal

sperm counts were reduced by 90%. Analysis of the reproductive tract at sacrifice revealed that accessory organ (prostate, seminal vesicle, vas deferens) weights were essentially unchanged; however, the weight of the testis, epididymis and cauda epididymus were significantly reduced. Histopathological analyses revealed that pachytene spermatocytes were the most susceptible to 2-ethoxyethanol at levels that apparently induce few clinical symptoms.

Nagano et al. (1979) investigated the testicular effects of orally administered 2-ethoxyethanol given at doses of 500, 1000, 2000 or 4000 mg/kg, 5 days/week, for 5 weeks to JCL-ICR mice. There was a dose-related decrease in absolute and relative testes weight; the 1000 mg/kg treatment group exhibited the first significant changes. Histological alterations at the 1000 mg/kg dose level included atrophy of the seminiferous tubules and a marked reduction in the number of spermatocytes, spermatids, and spermatozoa. A greater degree of atrophy was observed in the testes of animals exposed to 2000 mg/kg. These mice also had a decrease in seminiferous tubule diameter, an increase in interstitial tissue and the almost complete absence of spermatozoa and spermatids. Exposure to a concentration of 2.5% 2-ethoxyethanol in the drinking water for 18 days also resulted in depressed testicular weights (Nagano et al., 1979).

A study in the Russian literature by Syrovadko and Malysheva (1977) reported that women engaged in the production of enamel-insulated wires, which exposed them to a mixture of chlorobenzene, tricresol and 2-ethoxyethanol, experienced increased incidences of menstrual disorders and birth defects such as cardiovascular and foot anomalies. This study is difficult to interpret since 2-ethoxyethanol exposure was not quantitated. Furthermore, the Chemical Manufacturers Association's Glycol Ethers Program Panel

concluded that the study was significantly flawed and of little value to an assessment of human risk (CMA, 1983). It is mentioned here only for the sake of completeness.

Atrophy of germinal epithelium and testicular edema were observed in nearly two-thirds of albino rats fed diets containing 1.45% of (~900 mg/kg/day) in a 2-year study by Morris et al. (1942).

5.5. CHRONIC AND SUBCHRONIC EFFECTS

A 2-year feeding study in albino rats was conducted by Morris et al. (1942) using a dietary level of 1.45% 2-ethoxyethanol (~725 mg/kg/day). No differences in mortality, growth rate or food consumption were observed for the first 55 weeks of the study compared with control. Pathological changes in the lungs, heart, spleen, lymph nodes, pancreas, stomach, intestines and adrenals were no different than those seen in control animals. 2-Ethoxyethanol exposed animals showed testicular enlargement, edema and tubular atrophy. The authors stated that two-thirds of the animals were affected.

A 2-year study conducted by Gulf South Research Institute (Melnick, 1984) examined the toxicity of 2-ethoxyethanol in male and female F344/N rats and B6C3F1 mice. Animals were gavaged with 0.5, 1.0 or 2.0 g/kg, 5 days/week for 103 weeks. The high dose group had a high mortality rate, and the surviving animals were sacrificed between weeks 17 and 18. Testicular degeneration was also evident in the medium and high dose mice and in the 2 g/kg group in rats. In addition, an increased incidence of enlarged adrenal glands was also observed at the two lower dose levels in male rats (statistics not reported). Survival of medium dose male rats was also reduced; females from this dose group were not adversely affected.

Rats receiving 2-ethoxyethanol in the drinking water for 90 days at a dose of 210 mg/kg/day displayed no overt signs of toxicity. An intermediate dose of 740 mg/kg/day resulted in altered weights and microscopic lesions in the liver and kidney as well as a reduction in body weight gain and food consumption, while a dosage level of 1.89 g/kg/day produced increased mortality (Smyth et al., 1951). In another 90-day study, 0.25% 2-ethoxyethanol in the diet had no effect while 1.25% resulted in weight reduction in rats (Rowe and Wolf, 1982).

Male JCL-ICR mice were intubated with 4000, 2000, 1000 or 500 mg/kg 2-ethoxyethanol 5 days/week for 5 weeks. A significant dose-related decrease in white blood cell count was observed in these animals. Leukopenia was also demonstrated in mice given 2.5% 2-ethoxyethanol in the drinking water for 18 days. These animals also had significantly reduced body weights following treatment compared to the control group (Nagano et al., 1979).

Stenger et al. (1971) examined the subchronic effects of oral and s.c. 2-ethoxyethanol exposures in Wistar rats and oral doses in beagle dogs. Rats were injected s.c. with 0, 100, 200, 400 or 800 μ l/kg/day for 4 weeks. At the two highest doses, signs of dyspnea, somnulence and ataxia were observed. Hemoglobin and hematocrit values were not remarkably affected. Similar groups of male and female rats were treated with 0, 50, 100 or 200 μ l/kg/day for 13 weeks or with 100 and 200 μ l/kg/day for the first 58 days and 400 or 800 μ l/kg/day, respectively, for the remaining 33 days. Only those animals in the latter two treatment groups showed depressed hemoglobin [19% reduction (i.e., 15.6 vs. 12.6) in the 100/400 μ l/kg group and 30% reduction (i.e., 15.6 vs. 11.0) in the 200/800 μ l/kg group] and hematocrit [15% (i.e., 49 vs. 42) and 20% (i.e., 49 vs. 39) decreases, respectively] values by week 13.

Beagle dogs were fed gelatin capsules containing 0, 50, 100 or 200 $\mu\text{L/kg}$ 2-ethoxyethanol daily for 13 weeks. By week 13, dogs in the 200 $\mu\text{L/kg}$ treatment group had a 22% reduction in hemoglobin concentrations and a 24% decrease in hematocrit.

Histopathological examination of these rats and dogs revealed changes primarily located in the testes, livers and kidneys of both species. Testicular damage in the form of interstitial edema and the marked reduction or absence of late spermatocyte maturation was noted in rats treated s.c. with 400 and 800 $\mu\text{L/kg}$ 2-ethoxyethanol. Also observed in these treatment groups were alterations in the lobular structure of the liver and swelling of epithelia and narrowing of lumina in kidney tubules. Rats treated orally with 200 or 200/800 $\mu\text{L/kg}$ showed similar dose-related alterations in the testes, liver and kidney. In addition, there were significant quantities of hemosiderin deposits in the spleens of these animals. In dogs exposed to 200 $\mu\text{L/kg}$ orally for 13 weeks, dilation of tubules in the testes and azoospermia were noted. In addition, 50% of the animals in this group had moderate alterations characterized by dilated lumina and flattened epithelia in the tubules.

A subchronic inhalation study was conducted by Barbee et al. (1984) using male and female Sprague-Dawley CD rats and New Zealand White rabbits. Animals were exposed to 0, 25, 100 or 400 ppm 2-ethoxyethanol, 6 hours/day, 5 days/week for 13 weeks. Only rabbits in the 400 ppm group had a dose-related decrease in weight gain as compared to air-treated control animals. Significant alterations in organ weights were isolated and not dose-related. Hematological measurements revealed a significant decrease in hemoglobin, hematocrit, and red blood cell count in rabbits treated with 400 ppm. The only histopathological change noted was slight testicular degeneration in rabbits.

Dogs were exposed to 840 ppm (3095 mg/m³) 2-ethoxyethanol, 7 hours/day, 5 days/week, for 12 weeks in a study conducted by Werner et al. (1943a). Although only two animals were exposed to the compound, hematological changes similar to those seen in rats (Werner et al., 1943a) were seen, most notably a significant increase in the number of immature granulocytes in the blood. Furthermore, the concentration of oxalate in the urine was significantly increased.

Adult Wistar rats (male and female) were exposed to 370 ppm (1370 mg/m³) 2-ethoxyethanol 7 hours/day, 5 days/week for 5 weeks. Animals were sacrificed throughout the exposure period and up to 3 weeks following the termination of exposure. No significant changes in body weight or mortality were noted at any time point during the study. Similarly, there were no differences in lung, kidney or heart parameters compared to controls. In the spleen, there was a doubling of the hemosiderin content and a significant decrease in the amount of myeloid tissue. Additionally, the proportion of juvenile granulocytes in the blood was significantly increased relative to control animals. This increase was obvious after only 1 week of exposure. The pathological and hematological variations were generally reversible after cessation of exposure (Werner et al., 1943a).

5.6. OTHER RELEVANT INFORMATION

The acute effects of 2-ethoxyethanol in a number of species are summarized in Table 5-2. Single oral exposures did not produce immediate overt symptoms; however, pathological examination revealed hemorrhage in the gastrointestinal tract, extreme kidney injury, moderate liver damage and hematuria in mice, rats, and guinea pigs (Laug et al., 1939).

TABLE 5-2
Acute Toxicity of 2-Ethoxyethanol

Route	Species	Dose (g/kg)	Response	Reference
Oral	rats	3.22 (3.05-3.37)	LD ₅₀ (95% confidence interval)	Laug et al., 1939
	rats (male) (5-6 weeks old)	5.0	LD ₅₀ : death of 50% within 14-day period	Carpenter et al., 1956
	rats (female)	5.4	LD ₅₀	Carpenter et al., 1956
	rats (female)	5.5	LD ₅₀	Carpenter et al., 1956
	rats	3.0	LD ₅₀ : death delayed 1 week	Smyth et al., 1941; Union Carbide, 1976
	rats (male)	2.3	LD ₅₀ : 14-day observation period	Cheever et al., 1984
	rats	4.5	LD ₅₀	Stenger et al., 1971
	rats	1.09	LD ₅₀	Patty, 1963
	mice	4.8	LD ₅₀	Stenger et al., 1971
	mice	4.0 (3.73-4.32) (concentrated solution)	LD ₅₀	Laug et al., 1939
	mice	4.84 (4.40-5.33) (1:1 dilution)	LD ₅₀ (95% confidence interval)	Laug et al., 1939
	mice	3.5 (in oil solution)	LD ₅₀	Saparmamedov, 1974
	mice	4.8	LD ₅₀	Stenger et al., 1971
Oral	guinea pigs	2.6 (2.39-2.81)	LD ₅₀ (95% confidence interval)	Laug et al., 1939
	guinea pigs	1.4 (10% solution)	LD ₅₀	Carpenter et al., 1956
	guinea pigs	2.14	LD ₅₀	Stenger et al., 1971
	rabbits	1.5	LD ₅₀	Stenger et al., 1971
	rabbits	3.1	LD ₅₀	Carpenter et al., 1956
	rats	1.2	Average lethal dose; narcosis, urinary incontinence, diarrhea, respiratory distress, liver damage, peritoneal adhesions	Sanderson, 1959
	i.p.			

TABLE S-2 (cont.)

Route	Species	Dose (g/kg)	Response	Reference
i.p. (cont.)	rats	2.0 (undiluted)	LD ₅₀	Carpenter et al., 1956
	rats	2.6	LD ₅₀	Stenger et al., 1971
	mice	1.7	LD ₅₀ (observation period of 7 days)	Karel et al., 1947
s.c.	rats	4.65	LD ₅₀	von Oettingen and Jirouch, 1931
	rats	3.16	LD ₅₀	Stenger et al., 1971
	mice	2.3	LD ₅₀	Stenger et al., 1971
i.v.	rabbits	1.85	LD ₅₀	Stenger et al., 1971
	rats	3.25 (10% solution)	LD ₅₀	Carpenter et al., 1956
	mice	3.6	LD ₅₀	Stenger et al., 1971
	rats	2.7	LD ₅₀	Stenger et al., 1971
	mice	3.9	LD ₅₀	Stenger et al., 1971
	rabbits	0.8	LD ₅₀	Stenger et al., 1971
	cats	1357 ppm 8 hours/day; 4.5 days	LC ₅₀	WIOSH, 1979
Inhalation				Brouning, 1965
	rats (male or female)	4000 ppm for 4 hours	Killed 2/6, 3/6 or 4/6 within 14 days	Carpenter et al., 1956
	rats	125 ppm for 4 hours	Increased fragility of red blood cells	Carpenter et al., 1956
	rats	2000 ppm for 4 hours	LD ₅₀	Sax, 1979
	rats	4000 ppm for 8 hours	100% mortality (range finding)	Carpenter et al., 1956
	rats	2000 ppm for 8 hours	LC ₅₀ (range finding)	Carpenter et al., 1956
	rabbits	1357 ppm for 8 hours/day; 12 days	LC ₅₀	Brouning, 1965
	mice	1820 ppm for 7 hours	LC ₅₀ : death within 1 week	Werner et al., 1943a

TABLE 5-2 (cont.)

Route	Species	Dose (g/kg)	Response	Reference
Inhalation (cont.)	mice	2210 ppm for 7 hours	LC ₅₀ : death within 32 hours	Werner et al., 1943a
	mice	1357 ppm for 8 hours/ day; 5 days	LC ₅₀	Browning, 1965
Inhalation	guinea pigs	0.3% for 24 hours	5/6 dead 24 hours after exposure	Matte et al., 1930
	guinea pigs	>6000 ppm for 1 hour	LC ₅₀	Browning, 1965
Dermal	rabbits	3.56 ml/kg (undiluted)	LD ₅₀ (contact with clipped) skin for 24 hours; observation period of 14 days)	Carpenter et al., 1956
Ocular	rabbits	90 mg	Moderate injury	Carpenter et al., 1956
		one drop (undiluted)	Hyperemia and edema of conjunctiva	von Gelltingen and Jirouch, 1931
	guinea pigs	0.01 ml	Irritation	Sanderson, 1959

Waite et al. (1930) examined the acute inhalation effects of 2-ethoxyethanol in guinea pigs. Guinea pigs tolerated 6000 ppm for 1 hour, 3000 ppm for 4 hours or 500 ppm for 24 hours without exhibiting toxic effects. Higher exposure regimens resulted in lung and kidney injury as well as hemorrhage in the gastrointestinal tract.

In mice, acute inhalation exposure to 2-ethoxyethanol resulted in lung congestion and edema as well as kidney, stomach, and spleen damage (Werner et al., 1943c). Stenger et al. (1971) investigated acute LD₅₀ values in mice, rats, guinea pigs, and rabbits and over an 8-day observation period observed signs of dyspnea, somnolence, ataxia and seizures.

An oral LD₁₀ for female CD-1 mice of 3605 mg/kg was established by observing the animals during an 8-day dosing period and an 8-day post-exposure period (Schuler et al., 1984). Administration of 2-ethoxyethanol via gavage, 5 days/week for 2 weeks to male and female F344/N rats and B6C3F₁ mice resulted in 100% mortality at a 5 g/kg/day level and 100% survival at 1.25 g/kg/day (Melnick, 1984).

An odor threshold of 125 ppm and an intolerable level of >255 ppm for 2-ethoxyethanol vapors in human volunteers was established. This indicates, therefore, that the detection of 2-ethoxyethanol odor should not be assumed to be protective against chronic inhalation exposure to 2-ethoxyethanol (Rowe and Wolf, 1982).

2-Ethoxyethanol can cause significant eye and skin irritation. Inhalation of sufficiently high vapor concentrations can result in headache, nausea, vomiting and diarrhea (Shell Oil, 1978).

Female SPF Sprague-Dawley rats were treated dermally with 0.35 ml undiluted 2-ethoxyethanol 1, 2 or 4 times/day for 10 consecutive days. All animals were sacrificed 5 days after the completion of treatment and examined for signs of toxicity. The only changes observed were ataxia during the last 2 days of treatment in the highest dose group and on day 10 of treatment in the 1.4 ml/day group. Mean body weights and kidney and liver weights were unaffected (Hardin et al., 1982).

The effects of 2-ethoxyethanol on cell-mediated immunocompetance was investigated by Houchens et al. (1984) using allogeneic B6C3F₁ and syngeneic CD2F₁ mice. Allogeneic mice were treated orally with 2-ethoxyethanol at 600, 1200 or 2400 mg/kg on 12-8 and 5-1 days prior to challenge with L1210 mouse leukemia cells. Syngeneic mice were similarly treated on days 1-5 and 8-12 after challenge with leukemia cells. The two higher doses of 2-ethoxyethanol reduced the average body weight gain in the CD2F₁ mice, although the results were not statistically significant. No direct protection against the leukemia cells was observed in these mice at any dose level. The results in the allogeneic mice appeared to suggest that 2-ethoxyethanol may exert a prophylactic effect by inducing the immune system.

2-Ethoxyethanol enhanced the efficacy of arabinosylcytosine, an antiviral and tumor-growth inhibiting chemotherapeutic agent, by inhibiting the enzymatic deamination of the drug (Camlener and Tao, 1968).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Data on the acute toxicity of 2-ethoxyethanol to aquatic organisms are limited. Bridle et al. (1979b) conducted a preliminary investigation into the toxicological response of the goldfish, Carassius auratus, to 2-ethoxyethanol under static test conditions. A 24-hour LC_{50} >5000 mg/l was determined (Table 6-1). Using a standardized static procedure, Dawson et al. (1977) determined the 96-hour LC_{50} values to be $>10,000$ mg/l for both the freshwater bluegill, Lepomis macrochirus, and the marine tidewater silverside, Menidia beryllina, (see Table 6-1). Konemann (1981) used a 24-hour renewal procedure in the determination of the 168-hour LC_{50} of 16,377 mg/l for the guppy, Poecilia reticulata.

The acute toxicity of 2-ethoxyethanol to the water flea, Daphnia magna, was investigated by Hermens et al. (1984) under static conditions (Table 6-2). The concentration of test material required to cause immobilization in 50% of the organisms exposed (IC_{50}) over a 48-hour period was determined to be 7660 mg/l.

6.2. CHRONIC TOXICITY

Johnson et al. (1984) investigated the toxicological effects of 2-ethoxyethanol on adult and developing hydra, Hydra attenuata. Approximately 700-1000 adult hydra were collected and dissociated mechanically into their component cells. The cells were then randomly reassociated into gently packed small pellets through low-speed centrifugation. Such reaggregated cells undergo a full ontogenesis sequence. The ontogenesis sequence is completed in 92 hours, giving rise to a new population of adult polyps.

The MEC of 2-ethoxyethanol capable of producing adult and developing toxicity was determined to be 30 and 6.0 ml/l, respectively (see Table

TABLE 6-1
Acute Lethal Effects on 2-Ethoxyethanol to Freshwater and Marine Fish

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Goldfish <u>Carassius auratus</u>	24	>5,000	20±1°C; static	LC50	Bridle et al., 1979b
Bluegill <u>Lepomis macrochirus</u>	96	>10,000	23°C; static	LC50	Dawson et al., 1977
Tidewater silversides <u>Menidia beryllina</u>	96	>10,000	20°C; static	LC50	Dawson et al., 1977
Guppies <u>Poecilia reticulata</u>	168	16,377	22±1°C; renewal	LC50	Konemann, 1981

TABLE 6-2
Acute and Chronic Effects of 2-Ethoxyethanol to Aquatic Invertebrates

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Water flea <u>Daphnia magna</u>	48	7660	22±1°C; static	IC50	Hermens et al., 1984
<u>Hydra attenuata</u> ; adult	--	30.0	--	MEC	Johnson et al., 1984
<u>Hydra attenuata</u> ; Artificial "embryo"	--	60.0	--	MEC	Johnson et al., 1984

6-2). Although the duration of exposure was not provided for either the adult or developing hydra, the exposure may have occurred throughout the 92-hour ontogenesis sequence.

6.3. PLANT EFFECTS

Data on the effects of 2-ethoxyethanol on aquatic plants were not located in the available literature cited in the Appendix.

6.4. RESIDUE

Data on 2-ethoxyethanol residues in aquatic organisms were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Rebhun and Sawada (1969) investigated the effects of 2-ethoxyethanol on the structure of the mitotic apparatus of the surf clam, Spisula solidissima, and sea urchin, Lytechinus, eggs. A 2-ethoxyethanol concentration of 150 ml/l in seawater caused an increase of ~50% in length and 200% in width of the isolated mitotic apparatus. In addition, exposure to ethoxyethanol also caused the formation of the central aster from the first polar body mitotic apparatus by a shortening of the spindle and fusion of the asters to form a large central monaster. A second polar body mitotic apparatus formed from this central monaster which was ~50% longer and 300% wider than those of the control first or second polar body mitotic apparatuses.

The immediate effects of 2-ethoxyethanol were reversible, but reversibility of effects on embryonic development was only obtained if the eggs did not remain exposed to the compound for too long a period (maximum acceptable exposure was not reported). Although no definitive determination of mode of action was made, the authors, based on effects on mitotic apparatus which is crucial for sperm development, suggested that 2-ethoxyethanol acted indirectly on the mitotic apparatus.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists recently adopted a revised 5 ppm (18 mg/m³) for 2-ethoxyethanol (ACGIH, 1984). This level is based in part on the current TLV for 2-methoxyethanol although 2-ethoxyethanol is somewhat less toxic (ACGIH, 1980). OSHA has established a TLV of 200 ppm (Code of Federal Regulations, 1981). Both of these recommendations are accompanied by the "skin" notation indicating that dermal absorption is a potentially harmful route of exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 2-ethoxyethanol were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Two long-term studies in which 2-ethoxyethanol was administered either in the diet (Morris et al., 1942) or via gavage (Melnick, 1984) for 2 years at doses up to 1.0 g/kg/day did not result in any increased tumor incidence in mice and rats. In addition, 2-ethoxyethanol is nonmutagenic in reverse mutation assays performed by several laboratories (Ong, 1980; Ong et al., 1980; Zeiger et al., 1982; Szybalski, 1958; Kawalek and Andrews, 1980).

Acute, subchronic and chronic studies have revealed that 2-ethoxyethanol mainly exerts effects on the blood, liver, kidneys, testes, spleen, and developing fetus. Although 2-ethoxyethanol has clearly been shown to be a teratogen, few studies have examined the effects of oral dosing. Stenger et al. (1971) demonstrated an apparent decrease in mean fetal weight and an increased incidence of skeletal abnormalities after oral administration of 93-372 mg/kg/day and an apparent increase in fetal and embryonic mortality at doses of 186 and 372 mg/kg/day, respectively. The compound was administered to Wistar rats during the first 21 days of gestation. A dose of 46.5 mg/kg/day produced no effects in this study. The authors judged the 93 mg/kg dose to be a LOAEL. Although data were completely reported, no statistics were presented. Cardiovascular anomalies, depressed fetal weights, and increased embryomortality was observed in Sprague-Dawley rats given 200 mg/kg/day orally during shorter intervals of pregnancy (Goad and Cranmer, 1984). No mention of maternal toxicity was made in either study.

Inhalation appears to be the preferred route of exposure in studies designed to investigate the effects of 2-ethoxyethanol on fetal development. Sprague-Dawley rats exposed to atmospheres containing 737-4422 mg/m³ 2-ethoxyethanol for 7 hours/day during either days 7-13 or 14-20 of gestation had dose-dependent increased incidences of neonatal deaths (Nelson et

al., 1981). Exposure of these rats to 369 or 737 mg/m³, 7 hours/day during the same gestation periods resulted in neurochemical and behavioral alterations in surviving offspring (Nelson et al., 1982a,b). Doe (1984a) observed fetotoxic and teratogenic effects in fetuses from rats exposed to 184 or 921 mg/m³ 2-ethoxyethanol, 6 hours/day during days 6-15 of gestation; however, no effects were observed at 37 mg/m³. No effects were observed at 184 mg/m³, 6 hours/day in rabbits exposed during gestation. A higher concentration (645 mg/m³) resulted in a number of skeletal defects. The only maternal effects observed were in the high-dose rat group which had decreases in hemoglobin, hematocrit, and mean red blood cell volumes.

New Zealand rabbits exposed to 2274 mg/m³ 2-ethoxyethanol, 7 hours/day during days 1-18 of gestation and Sprague-Dawley rats exposed to 2826 mg/m³ 2-ethoxyethanol, 7 hours/day during gestation days 1-19 had no viable litters (Andrew et al., 1981). Using the same exposure regimen, rabbits exposed to 590 mg/m³ had increased embryomortality and fetuses with increased numbers of visceral and skeletal abnormalities, while rats inhaling 744 mg/m³ had fetuses with depressed weights and minor skeletal and cardiovascular anomalies. Animals in the high exposure groups showed overt signs of maternal toxicity while only rabbits in the low-dose group had minor signs of toxicity manifested mostly as changes in organ weights.

Dermal exposure in pregnant SPF Sprague-Dawley rats to 931-1862 mg/day during gestation days 7-16 resulted in increased resorptions, fetotoxicity and visceral and skeletal malformations. Maternal toxicity as evidenced by altered liver and kidney weights, depressed body weight gain and ataxia was observed in the high-dose group only (Hardin et al., 1982, 1984).

Oral treatment of CD-1 mice with 2600 mg/kg/day (authors' estimate) of 2% ethoxyethanol in the drinking water over a 15-week period resulted in the production of no viable litters (Lamb et al., 1984). A 2-ethoxyethanol

concentration of 1% in the drinking water (1500 mg/kg, authors' estimate) of male or female CD-1 mice over a 15-week period resulted in significant impairment in fertility and reproductive performance. No effects were observed at a drinking water level of 0.5%. The authors did not estimate a dose for this group but by analogy to the 1% group, in which drinking water consumption was reported to not be suppressed, a dose of 750 mg/kg/day can be estimated (Lamb et al., 1984).

A number of studies have demonstrated that the testes are especially sensitive to 2-ethoxyethanol. Rats given 186 mg/kg/day orally for 13 weeks had testicular edema and spermatocyte degeneration, while no effects were observed at a dose of 93 mg/kg/day. Similar results were obtained using dogs (Stenger et al., 1971). Rats receiving 936-2808 mg/kg/day for 5 days or the equivalent of 669 mg/kg/day over a 6-week period had decreased sperm counts and increased percentages of morphologically abnormal sperm (Zenick et al., 1984). Treatment of rats with oral doses of 2-ethoxyethanol ranging from 500-1000 mg/kg/day for 11 days resulted in decreased testicular weights and primary spermatocyte degeneration. A low dose of 250 mg/kg/day produced no detrimental testicular effects (Foster et al., 1983; Creasy and Foster, 1984).

Oral treatment of mice with doses equivalent to 714 or 1428 mg/kg/day for 5 weeks produced a dose-related decrease in testes weight and degeneration of seminiferous epithelium, while a drinking water concentration of 2.5% (~4250 mg/kg/day assuming a standard water consumption for mice of 0.17 L/kg) resulted in depressed testicular weights. No effects on testes were observed at 345 mg/kg/day (Nagano et al., 1979). Male mice that were given drinking water containing 1% and 2% 2-ethoxyethanol (estimated to be equivalent to daily doses of 1500 mg/kg and 2600 mg/kg, respectively) had

decreased testes weights and sperm motility and greater percentages of abnormal sperm. A level of 0.5% in the drinking water (~850 mg/kg/day, see above) had no apparent effect on the testes (Lamb et al., 1984).

New Zealand rabbits inhaling the equivalent of 2263 mg/m³, 6 hours/day, 5 days/week for 13 weeks had decreased testes weight and slight tubular focal degeneration. At a dose of 50 mg/kg/day calculated by the authors assuming 100% absorption of the inhaled 2-ethoxyethanol, no effects were observed (Barbee et al., 1984).

A number of short-term (90 days or less) studies have revealed the effects of 2-ethoxyethanol on other organs, such as liver, kidney, spleen, and the hemopoietic system. Oral doses of 2-ethoxyethanol of ≥ 186 mg/kg/day for 13 weeks caused the formation of splenic hemosiderin deposits in rats and kidney tubule alterations in dogs, while a dose of 93 mg/kg/day elicited decreases in hematocrit and hemoglobin concentration in both species. No effects occurred at 47 mg/kg/day (Stenger et al., 1971). Smyth et al. (1951) were able to cause microscopic lesions and altered weights in rat kidney and liver at a dose of 7400 mg/kg/day for 90 days but not at 210 mg/kg/day. Increased brain and spleen weights and depressed hematocrit and hemoglobin concentration resulted in rats given the equivalent of 669 mg/kg/day for 6 weeks, but this was the only dose level employed (Zenick et al., 1984). Male mice treated orally with 1428 mg 2-ethoxyethanol/kg/day for 5 weeks or 2.5% 2-ethoxyethanol in the drinking water (~4250 mg/kg/day, see above) for 18 days developed a decreased leukocyte count, while no effects were seen at 714 mg/kg/day was demonstrated (Nagano et al., 1979).

Inhalation studies have evoked similar responses. Concentration equivalent to 1474 mg/m³ 6 hours/day, 5 days/week over a 13-week period resulted in an altered hemogram in rabbits (Barbee et al., 1984). A 12-week exposure

to 3095 mg/m³, 7 hours/day, 5 days/week resulted in an altered hemogram in dogs (Werner et al., 1943a), while rats similarly exposed to 1370 mg/m³ for 5 weeks had an increased proportion of juvenile granulocytes in the blood and hemosiderosis in the spleen (Werner et al., 1943b).

Two chronic, oral studies of 2-ethoxyethanol toxicity have been conducted. Melnick (1984) administered 2-ethoxyethanol as gavage doses of 0, 0.5, 1.0 and 2 g/kg 5 days/week for 103 weeks. Fischer 344/N rats and B6C3F1 mice were used. Treatment and control groups included 50 animals/sex/species. Water was used as the vehicle. As a result of reduced survival the 2 g/kg groups (both sexes, both species) were terminated at weeks 17-18. The survival of male rats exposed to 1 g/kg was significantly reduced after 103 weeks of treatment. Survival of the female rats at both the 1 g/kg and 500 mg/kg groups was not significantly reduced. Survival of neither 500 mg/kg nor 1 g/kg exposed mice was affected. Mean body weights of mice were not adversely affected. Body weights of rats of both sexes in both the 500 and 1000 mg/kg groups appeared to be depressed (no statistical analysis).

High dose rats and mice (2 g/kg) showed testicular atrophy and stomach ulcers. Male rats in the 500 and 1000 mg/kg groups were reported to have increased incidences of enlarged adrenals (weight data not presented). No histopathological alterations were reported in female rats from the mid and low dose group or either sex of mice in the low dose group. Male mice from the mid dose group showed testicular atrophy. This study suggests a chronic LOAEL of 500 mg/kg/day based on reduced body weights in rats and an apparent increased incidence of enlarged adrenals in male rats. Since dosing was for 5 days of 7, multiplying by 5/7 results in an estimated TWA dose of 357 mg/kg/day.

Morris et al. (1942) administered 2-ethoxyethanol in the feed at a dietary level of 1.45% to albino rats for 2 years. There were 10 animals per treatment groups (6 males and 4 females). Assuming that rats consume 5% of their body weight per day in food, this feeding level would correspond to a dose of 725 mg/kg/day. No differences in body weights occurred. The only pathological change reported in the ethoxyethanol group was testicular enlargement, edema and tubular atrophy. The authors stated that these lesions occurred in "two-thirds" of the animals.

In summary, a NOAEL for rats was not established in either of the chronic studies. Melnick (1984) established the lowest LOAEL of 357 mg/kg/day associated with reduced body weight in male and female rats and possibly enlarged adrenals in male rats. Dividing this dose by an uncertainty factor of 10 to estimate a NOAEL results in a dose of 35.7 mg/kg/day which is below the subchronic NOELs including those based on fetotoxicity. Therefore, the dose of 35.7 mg/kg/day divided by an additional uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability) results in an ADI of 0.36 mg/kg/day or 25 mg/day for a 70 kg man.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The oral and inhalation toxicities for 2-ethoxyethanol are summarized in Table 9-1. Most studies were either conducted during gestation or for a period of no more than 90 days with only the Melnick (1984) and Morris et al. (1942) of chronic duration. Morris et al. (1942) demonstrated testicular atrophy in rats after daily exposure to 1.45% 2-ethoxyethanol in the diet (~725 mg/kg/day). The Melnick (1984) study involved dosing rats and mice with either 500, 1000 or 2000 mg/kg/day 5 days/week for 103 weeks. The highest dose produced testicular atrophy in rats and decreased survival in rats and mice; 1000 mg/kg/day resulted in decreased survival in male rats; and 500 mg/kg resulted in decreased body weights in rats. From these data, a human MED was calculated by multiplying the TWA daily dosages by the cube root of the body weight ratio (0.35 kg for rats, 0.03 kg for mice, 70 kg for humans) and by 70 kg to arrive at a daily dose for 70 kg man. The corresponding RV_d , RV_e , CS and RQ values can be found in Table 9-2.

The remaining studies dealing with 2-ethoxyethanol have used subchronic or gestational exposures. The more severe effects demonstrated involved damage to the fetus, impaired reproductive ability and decreased fetal survival. Stenger et al. (1971) established an MED for fetotoxicity of 93 mg/kg/day in rats. This corresponds to a human MED of 1113.2 mg/day and a CS of 14 (see Table 9-2). Doe (1984a) determined that doses of 50 ppm (184 mg/m³) for rats and 175 ppm (645 mg/m³) for rabbits 6 hours/day were sufficient to induce fetotoxicity and teratogenicity thus allowing the derivation of CS values for both species (see Table 9-2). Other studies have also produced harmful effects in the fetus using oral (Goad and Cranmer, 1984; Lamb et al., 1984; Schuler et al., 1984) and inhalation (Andrew et al., 1981; Nelson et al., 1981, 1982a,b) exposure (see Table 9-1 and Section 5.3.).

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TABLE 9-1
Toxicity Summary for 2-Ethoxyethanol

Route	Species/Strain	Sex	Number at Start	Vehicle/Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Oral	rat/SD	F	NR	water	NR	200 mg/kg/day, gestation days 7-9 or 10-12	200	Decreased fetal weight; increased cardiovascular anomalies	Goad and Cramer, 1984
		F	NR	water	NR	200 mg/kg/day, gestation days 7-15	200	Increased embryomortality; increased cardiovascular anomalies; decreased fetal weight	Goad and Cramer, 1984
	rat/Wistar CF	F	≥20	saline	NR	100 μl/kg/day, gestation days 1-21	93	Decreased fetal weight; increased skeletal abnormalities; increased fetal mortality	Stenger et al., 1971
	rat/Wistar CF	F	≥20	saline	NR	200 μl/kg/day, gestation days 1-21	186	Same as above	Stenger et al., 1971
Oral	rat/Wistar CF	F	≥20	saline	NR	400 μl/kg/day, gestation days 1-21	372	Same as above plus increased resorptions	Stenger et al., 1971
	rat/F344/N	M, F	50	water	>99%	2000 mg/kg/day, 5 days/week, 103 weeks	1429	Decreased testis weight; testicular atrophy; stomach ulcers; decreased survival	Meinick, 1984
	rat/F344/N	M, F	50	water	>99%	1000 mg/kg/day, 5 days/week, 103 weeks	714	Decreased weight; decreased survival in males; enlarged adrenal in males	Meinick, 1984
	rat/F344/N	M, F	50	water	>99%	500 mg/kg/day, 5 days/week	357	Decreased weight; enlarged adrenal in males	Meinick, 1984
Oral	rat/albino	NR	20	diet	NR	1.45% in diet for 2 years	725	Testicular enlargement, edema and tubular atrophy	Morris et al., 1942
Oral	mouse/CD-1	M, F	40	drinking water	99.4%	1% in drinking water, 1 week pre-mating, 14-week mating period	1500	Decreased reproductive performance; decreased fertility and reproductive performance in crossover matings; increased abnormal sperm	Lamb et al., 1984

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Vehicle/Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Oral	mouse/CD-1	M, F	40	drinking water	99.4%	2% in drinking water, 1 week pre-mating, 14-week mating period	2600	Decreased fertility and reproductive performance in crossover matings; no litters; increased % abnormal sperm; decreased testis weight; decreased % motile sperm	Lamb et al., 1984
Oral	mouse/CD-1	F	32	water	99%	3605 mg/kg/day, gestation days 7-14	3605	No viable litters produced	Schuler et al., 1984
Oral	mouse/B6C3F1	M, F	50	water	>99%	500 mg/kg/day, 5 days/week 103 weeks	357	Testicular atrophy	Meinick, 1984
Oral	mouse/B6C3F1	M, F	50	water	>99%	1000 mg/kg/day, 5 days/week 103 weeks	714	Testicular atrophy	Meinick, 1984
Oral	mouse/B6C3F1	M, F	50	water	>99%	2000 mg/kg/day, 5 days/week 103 weeks	1429	Testicular atrophy; stomach ulcers; decreased survival	Meinick, 1984
Inhalation	rat/SD	F	34	air/vapor	>99.9%	150 ppm, 7 hours/day, 50/week, 3 weeks; 202 ppm gestation days 1-19 7 hours/day	104	Increased fetal weight; decreased minor skeletal, cardiovascular, anomalies; decreased liver weight (maternal)	Andrew et al., 1981
Inhalation	rat/SD	F	34	air/vapor	>95.9%	649 ppm, 7 hours/day, 50/week, 3 weeks; 767 ppm gestation days 1-19 7 hours/day	416	100% resorptions; decreased liver weight (maternal); increased maternal lung, kidney weight	Andrew et al., 1981
Inhalation	rat/SD	F	2-6	air/vapor	98-98.5%	200 ppm, 7 hours/day, d.g. 7 hours/day	137	Increased neonatal deaths	Melson et al., 1981
Inhalation	rat/SD	F	2-6	air/vapor	98-98.5%	300 ppm, 7 hours/day, d.g. 7 hours/day	205	Increased neonatal deaths	Melson et al., 1981

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Vehicle/Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	rat/SD	F	2-6	air/vapor	98-98.5%	600 ppm, 7 hours/day, d.g. 7 hours/day	411	Increased neonatal deaths	Nelson et al., 1981
Inhalation	rat/SD	F	2-6	air/vapor	98-98.5%	900 ppm, 7 hours/day, d.g. 7 hours/day	616	100% resorptions	Nelson et al., 1981
Inhalation	rat/SD	F	2-6	air/vapor	98-98.5%	1200 ppm, 7 hours/day, d.g. 7 hours/day	823	100% resorptions	Nelson et al., 1981
Inhalation	rat/SD	F	15	air/vapor	98-98.5%	100 ppm, 7 hours/day, gestation days 7-13 or 14-20	69	Altered neurochemical levels and behavioral responses in offspring	Nelson et al., 1981
Inhalation	rat/SD	F	16	air/vapor	98-98.5%	200 ppm, 7 hours/day, gestation days 7-13 or 14-20	137	Same as above	Nelson et al., 1982a,b
Inhalation	rat/Alpk AP	F	24	air/vapor	>99%	50 ppm, 6 hours/day gestation days 6-15	29	Fetotoxicity	Boo, 1984a
Inhalation	rat/Alpk AP	F	24	air/vapor	>99%	250 ppm, 6 hours/day, gestation days 6-15	147	Fetotoxicity; minor visceral and skeletal malformations; decreased maternal hemoglobin, hematocrit and mean red blood cell volume	Boo, 1984a
Inhalation	rat/Wistar	MR	23	air/vapor	NR	370 ppm, 7 hours/day, 5 days/week, 5 weeks	181	Hemosiderosis in spleen; increased proportion of juvenile granulocytes	Werner et al., 1943d
Inhalation	rat/SD	M,F	30	air/vapor	99.6%	400 ppm, 6 hours/day, 5 days/week, 13 weeks	168	Decreased spleen weight (females)	Barbee et al., 1984
Inhalation	rabbit/WZ	F	29	air/vapor	>99.9%	160 ppm, 7 hours/day, gestation days 1-16	96	Increased visceral and skeletal abnormalities; increased embryo mortality; increased maternal liver, kidney weights	Andrew et al., 1981

TABLE 9-1 (cont.)

Route	Species/Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	rabbit/NZ	F	29	air/vapor	>99.9%	617 ppm, 7 hours/ day, gestation days 1-18	369	100% embryo mortality; increased maternal liver, kidney weights	Andrew et al., 1981
Inhalation	rabbit/Dutch	F	24	air/vapor	>99.9%	175 ppm, 6 hours/ day, gestation days 6-18	90	Fetal skeletal defects	Andrew et al., 1981
Inhalation	rabbit/NZ	M, F	20	air/vapor	99.9%	400 ppm, 6 hours/ day, 5 days/week, 13 weeks	146	Decreased hematocrit; de- creased hemoglobin; decreased mean red blood cell volume; decreased testis weight slight focal degeneration in testis	Andrew et al., 1981
Inhalation	dog/MR	MR	2	air/vapor	NR	840 ppm, 7 hours/ day, 5 days/week, 12 weeks	69	Altered hemogram	Werner et al., 1943b

TABLE 9-2
Composite Scores for the Toxicity of 2-Ethoxyethanol

Route	Species/Strain	Dosage/Exposure	Human MED (mg/day)	RV _d	Effect	RV _e	CS	RQ	Reference
Oral	rat/Wistar CF	50 µl/kg/day, gestation days 1-21	1113.2	1	fetotoxicity without maternal toxicity	8	8	1000	Stenger et al., 1971
Inhalation	rat/A6k AP	50 ppm, 6 hours/day, gestation days 6-15	347	1	Fetotoxicity without maternal toxicity	8	13.6	1000	Boe, 1984a
Inhalation	rat/A6k AP	250 ppm, 6 hours/day, gestation days 6-15	1760	1	Fetotoxicity without maternal toxicity	8	8	1000	Boe, 1984a
Inhalation	rabbit/Dutch	175 ppm, 6 hours/day, gestation days 6-18	2364	1	Fetal skeletal defects without maternal toxicity	10	10	1000	Boe, 1984a
Oral	mouse/CD-1	1% in drinking water, 1 week pre-mating, 14-week mating period	792 ^a	1.2	Decreased reproductive perform- ance; decreased fertility and reproductive performance in crossover matings; increased % abnormal sperm	8	9.5	1000	Lamb et al., 1984
Inhalation	rabbit/WZ	400 ppm, 6 hours/day 5 days/week, 13 weeks	384 ^a	1.6	Decreased testis weight; slight focal degeneration in testis	6	9.6	1000	Barbee et al., 1984
Oral	rat/F344H	2000 mg/kg/day, 5 days/week, 103 weeks	7542	1.0	Testicular atrophy; testicular edema	6	6.0	1000	Meinick, 1984
Inhalation	rat/SO	400 ppm, 6 hours/day, 5 days/week, 13 weeks	201 ^a	2.0	Decreased spleen weight	4	8.0	1000	Barbee et al., 1984
Inhalation	rabbit/WZ	400 ppm, 6 hours/day 5 days/week, 13 weeks	384 ^a	1.6	Decreased hematocrit, hemo- globin, mean red blood cell volume	4	6.4	1000	Barbee et al., 1984

^aUncertainty factor of 10 was incorporated to extrapolate a chronic human MED.

Table 9-2 summarizes those studies judged appropriate for the calculation of a CS and an RQ. Since adequate chronic oral studies are available, subchronic studies were not included unless they evaluated endpoints not adequately assessed in chronic evaluations. It should be emphasized that there is notable consistency among the CS values for each type of effect. The literature strongly suggests that the fetus and testis are most at risk from 2-ethoxyethanol either from oral or inhalation exposure and this is reflected in the generally higher CS values for those effects. The highest CS, 13.6, corresponds to fetotoxicity in rats exposed to 2-ethoxyethanol via inhalation (Doe, 1984a) (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The limited data pertinent to the carcinogenicity of 2-ethoxyethanol are insufficient to show a positive carcinogenic risk. Rats receiving ~725 mg/kg/day for 2 years did not have any observable tumors at the completion of the study (Morris et al., 1942). In another 2-year study rats and mice given 500, 1000 or 2000 mg/kg/day 5 days/week for 103 weeks had no reported increase in tumor incidence although histopathologic examinations are still ongoing (Melnick, 1984; NTP, 1984). Mutagenicity tests have been negative for the most part although two unpublished mammalian in vitro assays were reportedly positive (see Section 5.2.).

Using the IARC criteria for the weight of evidence of carcinogenicity, data on 2-ethoxyethanol are considered inadequate. Thus, 2-ethoxyethanol is most appropriately classified as a Group 3 chemical. Under current U.S. EPA (1984) guidelines, this chemical is classified as Group D. This indicates data are insufficient to determine the carcinogenicity of 2-ethoxyethanol to humans.

TABLE 9-3

2-ETHOXYETHANOL

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	347 mg/day
Effect:	Fetotoxicity
Reference:	Doe, 1984a
RV _d :	1.7
RV _e :	8
Composite Score:	13.6
RQ:	1000

*Equivalent human dose

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February, 1985, with the exception of the TOXLINE, which was searched and kindly supplied by the Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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